## REMARKS

Claims 1, 3, 5, 9, and 12-14 are pending in this application and stand rejected. Reconsideration is requested in view of the following remarks.

**Response to Claim Rejections Under 35 U. S. C. § 112, 2nd Paragraph**

All claims have been rejected as allegedly indefinite due the term "high" as describing the Aα chain integrity in claims 1 and 5. It is respectfully submitted that the term is not indefinite in view of the specification.

The relevant inquiry in determining whether a given claim satisfies the requirements of 35 USC 112, second paragraph, is whether the claim sets out and circumscribes a particular area with a *reasonable* degree of precision and particularity. *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not a precise as the examiner might desire. MPEP 2173.02. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (a) the contents of the particular application disclosure; (b) the teachings of the prior art; and (c) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *Id.* The fact that claim language, *including terms of* degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph. MPEP 2173.05(b). When considered in light of these factors, the expression "high Aα-chain integrity" is not indefinite.

Page 5, lines 4-15 of the specification discusses the differences between F1, F2 and F3 fibrinogen in terms of proteolytic damage to the carboxy-terminal region of the Aα chain of fibrinogen. The specification discloses that F2 has a lower molecular weight than F1 due to the aforementioned proteolytic damage. It is thus evident that a fibrinogen product with high Aα-chain integrity refers to a product with a high F1:F2 ratio. Page 10, lines 19-26 describes the method of the present invention that allows the selection of fibrinogen with regard to the integrity of the Aα-chain. It is possible to select fibrinogen product that comprises up to 100% fibrinogen.

Based upon these disclosures, and the knowledge of one of ordinary skill in the art, the expression "high Aα-chain integrity" is not indefinite.

All claims have been rejected as allegedly indefinite due the phrase "wherein the fibrinogen binds to the resin" in claim 1, asserting that it is unclear whether the phrase refers to "part-purified fibrinogen" in part (c) of claim 1, or the "fibrinogen from milk" of part (a) of the claim. It is clear from the claim that the "fibrinogen" which binds to the resin refers to the "part-purified fibrinogen", as this phrase appears earlier in the same sentence: "contacting the part-purified fibrinogen with a hydrophobic interaction chromatography resin under conditions wherein the fibrinogen binds to the resin".

It is respectfully submitted that claim 1 is not indefinite with respect to the meaning of the fibrinogen which binds resin.

**Response to Claim Rejections Under 35 U. S. C. § 103**

Claims 1, 3, 5, 9, and 12-14 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Garner *et al.* (US 5,639,940) in view of Tripodi (WO 9213495) Vukovich *et al.* (1980) and Lord, further in view of Holm *et al.* and Jennissen *et al.*

None of Garner, Tripodi, Vukovich or Lord teach or suggest a method for obtaining fibrinogen with high Aα chain integrity. Indeed, the term "Aα-chain integrity" does not even appear in any of the references, and the references do not recognize the advantage secured by the present invention in maintaining high Aα-chain integrity.

The deficiencies are not cured by Holm *et al.* or Jennissen *et al.* Even assuming the combination of these seven references, one would not expect to produce fibrinogen with high Aα-chain integrity. The fact that seven references are required to base the rejection is itself an indication of the patentability of the invention. *See, Adams v. United States*, 141 USPQ 361, 362 (US 1969) ("The volume of the prior art points to the novelty of the Adams invention.").

According to the present invention, fibrinogen is precipitated from milk, the precipitated fibrinogen is separated from protease enzymes, and part-purified fibrinogen is recovered (claim 1). Alternatively, milk derived from a transgenic animal is provided (claim 5). The part-purified fibrinogen or the transgenic animal milk is then contacted with a hydrophobic interaction chromatography (HIC) resin under conditions wherein the fibrinogen binds to the resin. Removal of the bound fibrinogen from the column by elution, which can occur in step-wise

fashion, provides for fractionation of the fibrinogen, thereby determining the composition of the resulting fibrinogen in terms of F1:F2 ratio. Fibrinogen of high Aα-chain integrity is selected.

Holm *et al.*, cited in present specification at page 6, line 24, describes the fractionation of already purified plasma fibrinogen by stepwise precipitation with ammonium sulfate in order to separate out and characterize HMW, LMW and LMW' fractions. In contrast to the present invention defined by claim 1, the Holm *et al.* precipitation step with ammonium sulfate is not being used to part-purify fibrinogen. The fibrinogen in the disclosure of Holm *et al.* has already been purified from human blood. Holm *et al.* use the ammonium sulfate precipitation step to fractionate plasma-derived fibrinogen into its component HMW, LMW and LMW' fractions. According to the invention defined by claim 1, precipitation is used to separate the fibrinogen from the damaging proteases found in the why fraction of milk. Fractionation of the fibrinogen is then achieved, not by ammonium sulfate precipitation, but by elution from an HIC resin.

The Examiner maintains that Holm *et al.* demonstrates that fibrinogen having high Aα chain integrity can be produced using precipitation, independently of HIC. According to the invention defined by claim 1, the aluminum sulfate precipitation step is used to separate fibrinogen from proteases in the whey phase of the milk, to prevent further proteolysis of the fibrinogen, not to fractionate the fibrinogen and select those fractions having high Aα chain integrity.

Jennissen *et al.* disclose a method for the production of fibrinogen from the blood of a diverse range of animals. Native biologically active fibrinogen is purified away from plasma in a single step. Plasma is applied to an HIC column, yielding purified fibrinogen. Examiner maintains that the molecular weight of the fibrinogen indicates that the fibrinogen chain is intact and can therefore be judge to have high integrity.

According to the present invention, HIC chromatography is used as a fractionation technique for resolving fibrinogen sub-fractions, i.e., F1, F2, F3, fragment Y and Fragment D and E, allowing removal of all of the Aα-chained fragments produced as a result of proteolysis in the source milk. Thus, fibrinogen with a high F1:F2 ratio and hence a high Aα-chain integrity is produced. Jennissen *et al.* does not describe the use of a HIC column to fractionate fibrinogen into its component forms and hence does not describe a method that separates intact fibrinogen

from fibrinogen degradation products (F2, F3, etc.) generated by the action of proteases. Thus, Jennissen *et al.* does not describe the production of fibrinogen with a high F1:F2 ratio, and hence a high Aα-chain integrity. Indeed, plasma fibrinogen is known to comprise only between 50 to 70% F1.

In addition, plasma-derived fibrinogen (as obtained by Jennissen *et al.*) does not contain all of the fibrinogen degradation products which occur in milk-derived fibrinogen as a result of the action of proteases in milk. Milk contains large amounts of casein, which comprises hydrophobic proteins that would be expected to disrupt the purification of fibrinogen from milk using HIC. Transgenic fibrinogen is under-sialylated compared to plasma-derived fibrinogen, due to the different glycosylation of the mammary gland. Thus, even if HIC could be used to fractionate plasma-derived fibrinogen (applicants submit that it can not), this would not indicate to one skilled in the art that HIC could effectively be used to fractionate milk-derived fibrinogen, particularly fibrinogen derived from the milk of transgenic animals as claimed in claim 5.

The nonobviousness of the present invention is even more apparent from the fact that others have suggested that HIC cannot be used to separate intact fibrinogen from degradation products:

> In the present investigation we first produced canine fibrinogen degradation products (FDP) following two optimized degradation protocols. These FDP-mixtures, which were alternatively enriched with X and Y fragments of D and E fragments, were purified further to individual FDP X, Y, D and E with over 95% purity by the means of two low pressure column chromatographic techniques (size exclusion chromatography and anionexchanger chromatography). With these techniques the FDP D could be separated into four different D subfractions. ***No satisfactory results were yielded by hydrophobic interaction chromatography (HIC)*** with C5-Alkysuperose, chromatofacusing and separations with hydroxyapatit. The observed strong binding of fragment E on hydroxyaptit probably points to the maintenance of the calcium binding site on the prepared canine E-fragment" (emphasis added).
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> Wolling *et al.*, *Berl. Munch Tierartz Wochenschr.* (1995); 108(11): 421-426 (emphasis added; copy enclosed).

Thus, it would not have been obvious to one of ordinary skill in the art to use HIC to separate F1 fibrinogen from fibrinogen degradation products. It would not have been obvious to use HIC to provide fibrinogen of with high Aα-chain integrity, from milk-derived fibrinogen, as provided by claims 1 and 5. Furthermore, for the reasons stated above, it would not have been obvious to one of ordinary skill in the art to combine the use of precipitation and HIC to produce

fibrinogen with high Aα-chain integrity, as set forth in claim 1. Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

**Conclusion**

Applicants respectfully submit that all pending claims are in condition for allowance. An early action toward allowance is earnestly solicited. The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will advance examination and allowance of the application.

Respectfully submitted,

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